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OFFICE OF
RESEARCH AND DEVELOPMENT

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MEMORANDUM

SUBJECT: Characterization of the IRIS Entries for Methyl Ethyl Ketone (MEK)

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This memorandum provides an evaluation of the current IRIS listings, in particular the inhalation reference concentration (RfC), for methyl ethyl ketone (MEK) in consideration of the current effort to delist MEK as a hazardous air pollutant (HAP). Current and other relevant information on MEK is also presented and its significance discussed. Also included is a commentary on the petitioner's proposal concerning the RfC.

Summary

The current noncancer IRIS listings for MEK

- are of low confidence primarily due to the lack of long-term toxicity data
- are imprecise as a consequence of this low confidence
- are within the range of values (i.e., the RfC) proposed by the Petitioner due to this imprecision
- have little basis to be substantively altered based on any new relevant information available since their initial derivation

MEK is currently listed on IRIS as "not classifiable as to human carcinogenicity". Limited occupational data exist that provide some suggestion of a cancer hazard for MEK. Neither the genotoxicity information on MEK nor the chemical structure of MEK support any readily apparent basis for a carcinogenic hazard.

There is scientific uncertainty surrounding the capacity of MEK to potentiate the toxicity of other compounds.

Characterization of IRIS MEK Assessments

The Agency evaluated MEK as part of the IRIS program in 1992-3 and developed an RfC of 1 mg/m^3 and an RfD of 0.6 mg/kg-day, with both values considered to be of low confidence. A principal reason for this confidence level (and consequential high overall uncertainty in the assessments) is the serious deficiencies in the data base of MEK, most notably the absence of lifetime studies. There exists no lifetime bioassay of MEK by any relevant route. Subchronic inhalation studies available for MEK provide a *de minimus* basis for establishment of an RfC but, because of various deficiencies including the lack of any clearly adverse effect level, could not be used to set the RfC. The RfC is based on effects reported in a short-term (10-day inhalation exposure) developmental study conducted at experimental concentrations of up to 2978 mg/m^3. The RfD is not derived from a study with MEK but was developed on a 2-generation reproduction study in which rats were administered 2-butanol, a chemical metabolically transformed into MEK.

The IRIS file for the RfC indicates that, by itself, MEK has little, if any, neurotoxic potential. *In vitro* laboratory results with isolated cultured cells and high concentrations of MEK do indicate that MEK has potential to produce neurotoxicity at the cellular level (Veronesi, 1984). Neurotoxicity is, however, not supported by animal studies. RfC documentation shows that no peripheral neurohistopathological changes were reported in rats exposed continuously to 3320 mg/m^3 MEK for up to 5 months (Saida et al., 1976). No treatment-related central or peripheral neurohistopathology was observed in rats exposed for 90 days (6 hrs/day, 5 days/week) at concentrations of MEK as high as 14,750 mg/m^3, even among animals specifically prepared and examined for neurohistopathology (Cavendar et al., 1983). Ten of ten rats exposed to MEK at 17,700 mg/m^{3}and higher, 8 hrs/day, 7 days/week, died in the 7th week of exposure without neurological symptoms or histopathology (Altenkirch et al., 1978).

A single long-term toxicity study of MEK has appeared since 1993, that of Mitran et al. (1997). This study reports neurotoxic effects among exposed workers (n = 41) as compared to nonexposed control subjects (n = 63). Objective (decrement in nerve conduction velocities compared to controls) and subjective (increased irritability, memory difficulties, bone and vertebral column pain) neurotoxic effects were reported among workers exposed for an average of 14 ± 7.5 years to MEK levels of 149-342 mg/m^3. This study has several serious methodological shortcomings in determination of nerve conduction velocity and in reporting of agents to which the workers may have been co-exposed. It is also acknowledged that the nature of the neurotoxicity implied by these results, distal axonal neuropathy, is not concordant with the molecular structure of MEK (Spencer et al., 1980; Graham, 2000). Nevertheless, total discounting of these data is imprudent due to the long-term duration of the exposure, the nature of the species (human) and the absence of any other empirical data countering these results. The MEK concentrations reported in the Mitran et al. (1997) study are below the current TLV of 590 mg/m^3 (200 ppm; ACGIH, 1989).

The IRIS file for the RfC does, however, discuss the capacity of MEK to potentiate neurotoxicity of other solvents. The nature of this potentiation is to decrease the exposure duration needed for the other solvents to produce the same adverse effect. MEK potentiation of solvent-induced polyneuropathies has been observed in humans with *n*-hexane (Vallat et al., 1981) and with glue containing light, volatile hydrocarbons (ATSDR, 1992). MEK potentiation of neurotoxicity has been confirmed in laboratory animals exposed to *n*-hexane (Altenkirch et al., 1983), methyl-*n*-butyl ketone (Saida et al., 1976), and ethanol (Cunningham et al., 1989). MEK also potentiated the hepatotoxicity of carbon tetrachloride (Traiger et al., 1989).

Several aspects of the phenomenon of potentiation are not clear including 1.) the relative proportions of MEK and the other neurotoxicant required for the potentiation to occur as well as 2.) the lower limits of the concentrations at which the potentiation would occur,. For example, the *n*-hexane:MEK proportions that resulted in potentiation were 4:1, 5:2, 3:2 (Altenkirch et al., 1978) although results indicating potentiation have been observed also with MEK in excess at 2:1 (Takeuchi et al., 1983). In the clinical case study of MEK potentiation reported by Vallat et al. (1981), the *n*-hexane:MEK proportion was reported as 8:20. The actual concentrations at which these potentiations may occur is also a source of uncertainty. With the *n*-hexane results in laboratory animal studies, combined concentrations of *n*-hexane and MEK of 1475- 2065 mg/m^3 were used. It is not clear if potentiation would be observed with lower ambient exposures to these mixtures either in humans or animals, i.e., the dose-response character of the potentiation is not known. The only information available on the dose-response of MEK potentiation is in rats with chloroform and carbon tetrachloride, not *n*-hexane (Raymond and Plaa, 1995). It is clear that MEK potentiation deals predominately with metabolic processes that are common to both experimental animals and man (ATSDR, 1992). Experimental evidence also exists to suggest that, at least in animals, the occurrence of potentiation becomes manifest only under chronic exposure conditions (Ichihara et al., 1998) not acute short-term exposures (van Engelen et al., 1997). These data on MEK potentiation may be especially relevant to consider in evaluation of the chronic toxic potential of exposures to mixtures containing MEK.

The evidence for MEK to be considered as "not classifiable as to human carcinogenicity" according to EPA's 1986 Cancer Guidelines MEK is based on a 1989 IRIS evaluation. This IRIS evaluation identified the lack of both animal and human data to assess the carcinogenic potential of MEK. At the current time, animal cancer bioassays with MEK by either the oral or inhalation route are still lacking. However, several human reports which assess MEK exposure were found in the literature. These reports included three retrospective cohort occupational studies of workers exposed to MEK (Alderson and Rattan, 1980; Wen et al., 1985; Blair et al., 1998 also as Spirtas et al., 1991) along with a case-control study of childhood leukemia which examined paternal exposures to several solvents including MEK (Lowengart et al., 1987). As a group, the cohort studies may be regarded as having very small cohorts and, hence, fewer numbers of cases from which to make conclusions for any cancer endpoint. The case-control study is considered more exploratory rather than testing a specific hypothesis. Together, the results from these limited studies provide some suggestion of a cancer hazard in humans. The genotoxicity information on MEK, however, does not indicate any readily apparent genetic mechanism for the action of MEK as the relatively complete spectrum of genotoxicity tests for MEK is essentially negative (ATSDR, 1992; Whittaker et al., 1990; Mayer and Goin, 1987).

Commentary on the Petitioner's Proposed revised RfC

Based on a reevaluation of the uncertainty factors in the current RfC, the Petitioner's have proposed a revised value for the RfC of 3.3 mg/m^3, a three-fold increase over the current IRIS RfC value of 1 mg/m^3.

There are two points of response to the Petitioner's proposal. First, IRIS re-evaluations are done in an integrated manner such that the entire database, oral and inhalation, cancer and noncancer, critical effects, uncertainty factors, etc., are simultaneously re-evaluated. Single components of the assessments, such as uncertainty factors, are not changed in an isolated manner without assurance that all other parts of the assessment are appropriately considered. There are no current plans for an IRIS reevaluation of MEK and no compelling reason, such as availability of information that would improve the database of the specific chemical (e.g. long-term chronic data), for undertaking a revision. Second, it should be kept in mind that the definition of RfC/D identifies clearly that these values are estimates that are within an order of magnitude of a safe level. One interpretation of the present MEK RfC at 1 mg/m^3 is that it is an estimate that could be as high as 3 mg/m^3 or as low as 0.3 mg/m^3. Although no consideration is given to the confidence level in this definition, the precision of low confidence assessments such as the RfD and RfC for MEK, would most certainly be considered worse than those for high confidence assessments. Taking into consideration these factors and interpretations, the revised estimate of the Petitioners of 3 mg/m^3 remains within the range of imprecision of this low confidence estimate and therefore is not different from the currently listed RfC.

References

ACGIH. 1989. TLVs Threshold limit values and biological exposure indices for 1989-1990. American Conference of Governmental Industrial Hygienists. Cincinnati, Ohio.

ATSDR. 1992. Toxicological Profile for 2-butanone. TP-91/08. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

Alderson, M. and N. Rattan. 1980. Mortality of workers on the isopropyl alcohol plant and two MEK dewaxing plants. Br. J. Ind. Med. 37: 85-89.

Altenkirch, H., G. Stoltenburg and H.M. Wagner. 1978. Experimental studies on hydrocarbon neuropathies induced by methyl-ethyl-ketone (MEK). J. Neurol.219: 159-170.

Blair, A., P. Hartge, P.A. Stewart, M. McAdams, J. Lubin. 1998. Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup. Environ. Med. 55: 161-171.

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg and E.J. Gralla. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3(4): 264-270.

Cunningham, J., M. Sharkawi, G.L. Plaa. 1989. Pharmacological and metabolic interactions between ethanol and methyl n-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, or acetone in mice. Fund. Appl. Toxicol.13(1):102-9.

Graham, D.G. 2000. Critical analysis of Mitran et al. (1997). Letter to the Editor. Environ. Res. 73: 181-188.

Ichihara, G., I. Saito, M. Kamijima, X. Yu, E. Shibata, M. Toida, and Y. Takeuchi. 1998. Urinary 2,5-hexanedione increases with potentiation of neurotoxicity in chronic coexposure to *n*-hexane and methyl ethyl ketone. Int. Arch. Occup. Environ. Health 71: 100-104.

Lowengart, R.A., J.M. Peters, C.Ciconi, J. Buckley, L. Bernstein, S. Preston-Martin, and E. Rappaport. 1987. Childhood leukemia and parents' occupational and home exposures. J. Natl. Cancer Inst. 79(1): 39-46.

Mayer, V.W. and C.J. Goin. 1987. Effects of chemical combinations on the induction of aneuploidy in *Saccharomyces cerevisiae*. Mutat. Res. 187: 21-30.

Mitran, E., T. Callender, B. Orha, P. Dragnea, and G. Botezatu. 1997. Neurotoxicity associated with occupational exposure to acetone, methyl ethyl ketone, and cyclohexanone. Environ. Res. 73(1-2):181-8.

Raymond, P. and G.L. Plaa. 1995. Ketone potentiation of haloalkane-induced hepato- and nephrotoxicity. I. Dose-response relationships. J. Toxicol. and Environ. Health 45: 465-480.

Saida, K., J.R. Mendell and H.S. Weiss. 1976. Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J. Neuropath. Exp. Neurol. 35(3): 205-225.

Spencer, P.S., H.H. Schaumberg, M.I. Sabri, and B. Veronesi. 1980. The enlarging view of hexacarbon neurotoxicity. CRC Crit. Rev. Toxicol. 7(4): 297-356.

Spirtas, R., P.A. Stewart, J.S. Lee, D.E. Marino, C.D. Forbes, D.J. Grauman, H.M. Pettigrew, A. Blair, R.N. Hoover, and J.L Cohen. 1991. Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br. J. Ind. Med. 48: 515-530.

Takeuchi, Y., Y. Ono, N. Hisanaga, M. Iwata, M. Aoyama, and J. Kitoh. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Br. J. Ind. Med. 40: 199-203.

Traiger, G.J. and J.V. Bruckner. 1976. The participation of 2-butanone in 2-butanol-induced potentiation of carbon tetrachloride hepatotoxicity. J. Pharmacol. Exp. Ther. 196: 493-500.

Vallat, J., M. Leboutet, A. Loubet, C. Piva, M. Dumas. 1981. *N*-hexane-induced and methylethylketone-induced polyneuropathy: abnormal accumulation of glycogen in unmyelineated axons. Acta Neutopathol. (Berlin) 55(4): 275-279.

van Engelen, J.G.M., W. Rebel-de Haan, J.J.G. Opdam and G.J. Mulder. 1997. Effect of coexposure to methyl ethyl ketone (MEK) on *n*-hexane toxicokinetics in human volunteers. Toxicol. Appl. Pharmacol. 144: 385-395.

Veronesi, B. 1984. An ultrastructural study of methyl ethyl ketone's effect on cultured nerve tissues. Neurotoxicology 5: 31-44.

Wen, C. P., S.P. Tsai, N. S. Weiss, R.L. Gibson, O. Wong, and W.A. McClellan. 1985. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. J. Natl. Cancer Inst.

Whittaker, S.G., F.K. Zimmerman, B. Dicus, W.W. Piegorsch, M.A. Resnick, and S. Fogel. 1990. Detection of induced chromosome loss in *Saccharomyces cerevisiae* - an interlaboratory assessment of 12 chemicals. Mutat. Res. 241: 225-242.